
Stem Cell-Mediated Oncocidal Therapy of Primary & Metastatic Brain Tumors

Grant Award Details

Stem Cell-Mediated Oncocidal Therapy of Primary & Metastatic Brain Tumors

Grant Type: Disease Team Planning

Grant Number: DT1-00696

Investigator:

Name:	Webster Cavenee
Institution:	Ludwig Institute for Cancer Research
Type:	PI

Award Value: \$3,867

Status: Closed

Grant Application Details

Application Title: Stem Cell-Mediated Oncocidal Therapy of Primary & Metastatic Brain Tumors

Public Abstract:

Brain tumors (BTs) are incurable, whether they start in the brain or spread there from other sites (e.g., lung, colon, breast, skin). Indeed, the latter situation is even more common & often more frustrating – although we've made inroads in treating such non-neural cancers, once brain metastases are discovered, hope is largely abandoned. Current therapies are limited by their inability to reach widely disseminated tumor cells that become insinuated within normal brain structures. Despite advances in surgical, radiation, pharmacologic, & gene therapies, survival with a BT remains dismal. Interestingly, the property that might circumvent this major obstacle to therapy – i.e., delivery of therapeutic molecules to the cells that need to be eliminated -- matches one of the better accepted attributes of the neural stem cell (NSC) – an attraction (over even great distances) for sites of pathology in the adult brain, including primary & metastatic cancer. If armed with a proper tumor-killing gene, the NSCs (whether administered into the brain or into the bloodstream), when drawn to these cancers, will dramatically reduce the tumor burden, including even single invading tumor cells, in a manner heretofore unachieved. The NSCs perform this action without themselves becoming tumorigenic or augmenting the pre-existing tumor. This phenomenon was 1st revealed by researchers on this proposed team. (In fact, the concepts have been extended to many other kinds of diseases.) In this proposal, a number of authentic mouse models of primary & metastatic BTs (including breast cancer) will be used (for this particular condition, we will not need a large animal model prior to clinical trials). Human NSCs (hNSCs) will be derived from 5 distinct sources, all have been proffered as being therapeutic but have never been compared head-to-head. Similarly a variety of potential hNSC-mediated therapeutic mechanisms will be compared. We anticipate a clinical trial of 1 or more of these cellular vehicles armed with the most effective gene for patients with intracranial BTs within ~3 yrs. Members of this proposed team have experience in bringing cancer therapies to clinical trial, hold the IP surrounding the use of stem cells against cancer, have begun negotiations with regulatory agencies, & have enlisted a GMP facility. Because immunocompatibility of the hNSCs with the recipient is not a concern in BT therapy, a limited number of hNSC lines need be developed for all prospective patients. Furthermore, BT treatment does not require long-term NSC survival or connectivity; can be piggy-backed onto present therapeutic regimes; is amenable to real-time imaging. Therefore, taken together, BTs may be the low hanging fruit of stem cell therapies. These concepts may ultimately be applicable to many kinds of cancers throughout the body using a range of different kinds of stem cells.

Statement of Benefit to California:

Brain tumors (BTs) are incurable, whether they start in the brain or spread there from other sites (e.g., lung, colon, breast, skin). Indeed, the latter situation is even more common & often more frustrating – although we've made inroads in treating such non-neural cancers, once brain metastases are discovered, hope is largely abandoned. The emotional & financial burden on California citizenry (the patients, their families, & the health care system) is immense. Despite advances in surgical, radiation, pharmacologic, & gene therapies, survival remains dismal. Current therapies are limited by their inability to reach widely disseminated tumor cells that become insinuated within normal brain structures. Interestingly, the property that might circumvent this obstacle to cure – i.e., delivery of therapeutic molecules to the cells that need to be eliminated -- matches one of the better accepted attributes of the neural stem cell (NSC) – an attraction (over even great distances) for sites of pathology. If armed with a proper tumor-killing gene, the NSCs (whether administered into the brain or into the bloodstream), when drawn to these cancers, will dramatically reduce the tumor burden, including even single invading tumor cells, in a manner heretofore unachieved. It has been suggested that BTs re-engage certain developmental programs operative in normal stem cells, hence making the latter well-poised to "hunt down" the latter because they might be responding to similar cues. (This "pathotropic" property of stem cells, first unveiled by members of this proposed team as been extended to many other kinds of diseases.) The concepts proposed in this application are eminently responsive to the RFA's goals in that they are mature & exploit known stem cell properties to address a therapeutic gap for a devastating disease unmet by extant approaches. BTs may be the low hanging fruit of stem cell therapies. The chances of a success – hence bringing credit to California's wisdom in passing Prop. 71 – are high (in part because the bar for success is so tragically low). We anticipate a clinical trial of a stem-cell based therapy for patients with intracranial BTs within ~3 yrs. Furthermore, this approach may ultimately be applicable to many types of cancers throughout the body using a range of different kinds of stem cells, a speculation already being validated by investigators & companies worldwide. If true, California may emerge as even a more prominent "Mecca" for cutting-edge cancer therapies. Furthermore, investigators on this proposed team have begun to understand some of the cues mediating the homing of NSCs to cancer. Although our initial clinical trial will focus on delivering genes already known to be effectively tumoricidal, new insights into the mechanisms underlying homing & metastasis may help identify novel therapeutic targets. Such insights could give rise to new intellectual property, in which California would be a stakeholder.

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